REMARKS

Summary of Response

In response to the Office Action dated July 11, 2007, Applicants filed a Notice of Appeal on January 9, 2008 and a three month Extension of time under 37 C.F.R. 1.136(a). Herewith, Applicants submit an Amendment and Request for Continued Examination (RCE) and a Three Month Extension of Time. Applicants respectfully submit the following Remarks.

Applicants have amended the claims to expedite prosecution. A summary of the Applicants Response to the Office Action dated July 11, 2007 are set forth below:

- Donahoe e*t al,* (U.S. Patent 5,661,126) does not teach interferon-γ as one of the chemotherapeutic agent which can be used as an agonist to MIS. Applicants respectfully submit that the present invention is not anticipated by Donahoe *et al.,* under §102, as Donahoe *et al.,* does not teach use of MIS in combination of decreased quantity of interferon-γ to reduce interferon-γ side-effects.
- Donahoe *et al,* (U.S. Patent 5,661,126) teaches an *inhibitor* of interferon-γ would be useful as an agonist of MIS. Applicants respectfully submit that the present invention is not anticipated by Donahoe *et al.,* under §102 as Donahoe et al, does not teach use of MIS in combination of decreased quantity of interferon-γ to reduce interferon-γ side-effects.
- MIS is effective at decreasing the dose of only selected chemotherapeutic agents. Without this knowledge, a skilled artisan would not be motivated to combine the teachings of Donahoe *et al* and Cohen *et al.,* nor would they have reasonably expected to succeed at the time of the present invention, and thus the present invention is not obvious by Donahoe *et al* in light of Cohen *et al.* anticipated under §103.
- Claims 1, 6-9, 18 and 16 have been amended to clarify the genus of fragments as those with ***substantially similar biological activity of MIS***. Applicants respectfully submit these amendments obviate the new matter §112 rejections.
- Claims 9 and 26 have been amended to correct an apparent typographical error with respect to "the amino acid SEQ …"

- Claims 9 and 26 have been amended to change the fragment to a C-terminal fragment of 109 amino acids to obviate the new matter rejection under §112.

Detailed Response

Claim Rejections under 35 U.S.C § 102

The Examiner has maintained the rejections to claims 1-11, 14-16, 18-28 and 31-33 as being anticipated by Donahoe *et al.*, (U.S. Patent Application 5,661,126) under 35 U.S.C § 102. The Examiner asserts that Donahoe *et al.*, teaches a method of treating tumors using the same reagents and the same method steps, and further asserts that Donahoe *et al.,* uses an effective amount of interferon-γ that results in decreased side effects, such as high fever and general weakness associated with interferon-γ.

Applicants respectfully disagree for the following reasons.

(1) As stated in the Response dated April 26, 2007, Applicants agree that Donahoe *et al.,* teaches the administration of chemotherapeutic agents to function as *agonists* to increase the anti-tumor effect of MIS. However, Applicants respectfully argue that Donahoe *et al.* does not specifically teach use of interferon-γ as one of the chemotherapeutic agents extensively listed (see column 21, lines 25 to 40) which can be used as an agonist to increase the anti-tumor effect of MIS.

Applicants also point out that interferon γ is highly distinct from both interferon α and interferon β on a structural and functional basis. As disclosed in paragraph [0069] in the present specification, Applicants teach that interferons are classified into two groups; either leukocyte and fibroblast derived Type I interferons, or as mitogen type induced or "immune" Type II interferons, and goes on to teach:

> "Type I interferons include interferon alpha (INF-α), interferon-beta (INF-β), interferon omega (INF-ω), interferon-tau (INF-τ) while Type II interferon includes interferon-gamma (INF-γ)."

Furthermore, interferon-γ was only known by persons skilled in the art as a cytokine or MHC Class I modulating molecule and not as a chemotherapeutic agent at the time of filing the current application. Accordingly, Donahoe *et al.,* does not teach use of decreased quantity of interferon γ for reduced side effects when interferon-γ as a therapeutic agent as claimed.

(2) Furthermore, the teachings in Donahoe *et al.*, would not teach a skilled artisan to use interferon-γ in combination with MIS for an additive effect on the treatment of the tumor. Rather, Donahoe *et al.*, teach an *inhibitor* of interferon-γ could be used as an agonist to MIS. For example, Donahoe *et al.*, teaches that MHC mRNA expression is upregulated by MIS and downregulated by EGF (see column 23, lines 43-45), and thus a skilled artisan would determine MIS and EGF have an inversely proportional effects on MHC expression. Accordingly, Donahoe *et al.*, teaches a skilled artisan to treat tumors with MIS and/or an agonist of MIS and/or an antagonist of EGF. However, on column 26, lines 34-36, Donahoe *et al.*, teach:

> "Examples of agonists of MIS include ***antibodies*** (or fragments… [of antibodies]) to ***EGF, interferon*** (α, β, γ), etc. ***EGF*** is an ***antagonist*** of MIS" (Emphasis added in bold italics).

Typically, a skilled artisan would know that an antibody which binds to a ligand, such as EGF or interferon-γ functions an *inhibitory antibody,* unless it is specifically taught otherwise. In fact, this exactly what Donahoe *et al.* teach in the statement that "EGF is an antagonist of MIS". Thus, a skilled artisan would know that an inhibitor of EGF, such as an *inhibitory antibody of EGF* would be useful to function as an agonists to MIS. Based on this teaching, a skilled artisan would also determine that an *inhibitory antibody of interferon-γ* would be useful to function as an agonists to MIS. Accordingly, Donahoe *et al.*, teaches the exact opposite of the present invention by teaching an *inhibitor* of interferon-γ would be useful as an agonist of MIS. Accordingly, Donahoe *et al.*, does not teach the use of interferon-γ in combination with MIS for an additive effect on the treatment of the tumor of the present invention, nor does it recite a method of treating tumors using the same reagents and the same method steps. Accordingly, Applicant respectfully submit that the renewed rejections of Claims 1-11, 14-16, 18-28 and 31-33 as being anticipated by Donahoe *et al.*, be withdrawn.

Claim Rejections under 35 U.S.C § 103

The Examiner has maintained the rejections to claims 1-11, 14-28 and 31-34 as being obvious over Donahoe *et al.,* (U.S. Patent Application 5,661,126) in light of Cohen *et al.,* (Int. J Radiation Oncology Biol Phys., 2/87, 13 (2);251-258) under 35 U.S.C § 102.

Applicants respectfully disagree for the reasons stated above. Applicants submit that Donahoe *et al.* does not teach use of interferon-γ in combination with MIS for an additive effect on the treatment of the tumor. Accordingly, as Donahoe *et al.,* does not teach use of interferon-γ, but rather an *inhibitor* of interferon-γ to increase the effectiveness of MIS for the treatment of tumors, a skilled artisan would not be motivated to combining and modifying Donahoe *et al.*, and Cohen *et al.*, in order to practice the claimed invention.

Furthermore, Applicants indicate that recent research by the inventors demonstrate that MIS can be used in combination only with *selected* targeted chemotherapies to enhance clinical efficacy and reduce toxicity (i.e. reduce dosage). For example, the inventors demonstrate in Pieretti-Vanmarke *et al.* (PNAS, 2006; 103; 17426-31), that MIS had a *competitive effect* and reduced the efficacy on inhibition of a growth of ovarian cancer cell lines of one of the four different chemotherapeutic drugs tested (i.e. rapamycin, pacilitaxel, cisplatin and doxorubicin). In particular, as shown in Figures 4G and 4H, while the combination of MIS and doxorubicin had a synergistic effect on inhibition of the MOVCAR7 (mouse ovarian cancer) cell line (Fig. 4G), the combination of MIS and doxorubicin had a *competitive effect* in 4306 cells, another different ovarian cancer cell line (Fig. 4H). Thus, a skilled artisan would readily determine that MIS in combination with a chemotherapy agent has varying effects, which is dependent at least in part, both on the tumor type and the specific chemotherapeutic agent. A skilled artisan would therefore determine that MIS cannot be used in combination with all chemotherapeutic agents to decrease the dose of such a chemotherapeutic agent, but rather MIS can be used in combination with selected chemotherapeutic agents after identification that MIS can function to decrease the dose and reduce the toxicity of such a chemotherapeutic agent in the cancer to be treated.

Accordingly, Applicants respectfully point out to Examiner that even ***if*** Donahoe *et al.* was found to teach the use of interferon-γ in combination with MIS to decrease the side-effects of interferon-γ, the combination of teachings of Donahoe *et al.*, and Cohen *et al.*, would not render the claimed invention obvious. This is because Donahoe *et al.* does not distinguish which chemotherapeutic agents can be combined with MIS to reduce their side effects, and in particular Donahoe *et al.,* does not teach the use of MIS in combination with carefully *selected* chemotherapeutic agents to reduce their side effects as discussed in Pieretti-Vanmarke *et al.*

Without such knowledge of *which* selected chemotherapeutic agents could be used in combination with MIS to reduce the dose, and thus the chemotherapy-associated side effects, Applicants assert that combining and modifying the teachings of Donahoe *et al.* and Cohen *et al.,* in order to practice the invention would not have reasonably be expected to succeed at the time of the present invention. Accordingly, Applicant respectfully submit that the renewed rejections of Claims 1-11, 14-28 and 31-34 be withdrawn.

Claim objections of Claims 9 and 26

The Examiner has objected to the amendments of Claims 9 and 26 for reciting an apparent typographical error. Applicants respectfully submit the amendments to claims 9 and 26 have obviated this objection.

New Matter Rejections under 35 U.S.C § 112, first paragraph (Written Description)

The Examiner raised new rejections to claims 1-11, 14-28 and 31-34 for failing to comply with the written description requirement under 35 U.S.C § 112, first paragraph.

The Examiner assert that claims 1, 6-8 and 18 recite a genus of fragments and asserts that they are not described in the specification which would reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time of filing.

Applicants respectfully disagree and indicate the specification teaches use of fragments of MIS. For example, in paragraphs [0065] and [0099] of the specification, Applicants teach:

> "The term "protein ***fragment***" is meant to include .... amino acid sequences ***derivable*** from the naturally occurring ***amino acid sequence of MIS***. The protein is said to be "derivable from the naturally-occurring amino acid sequence of MIS" if it can be obtained by ***fragmenting*** the naturally-occurring ***chosen sequence of MIS,*** or if it can be synthesized based ***upon a knowledge of the sequence*** of the naturally occurring amino acid sequence ... which encodes this sequence" (Emphasis added in bold italics).

Applicants also teach in paragraph [0063] of the specification;

> "... non-recombinant MIS or a ***fragment thereof***, ... can be used in the methods of the present invention." (Emphasis added in bold italics).

In paragraph [0081] of the specification, the Applicants teach:

> "The MIS of the present invention, its ***functional derivatives*** or its agonists, is provided in combination with interferon." (Emphasis added in bold italics).

Applicants indicate that the specification teaches in paragraph [0083] the following:

> "As used herein, unless specified otherwise, MIS is intended but not limited to the 140 kDa or 70 kDa MIS, C-terminal fragments of MIS and its ***functional derivatives***." (Emphasis added in bold italics).

The specification goes on to further teach in paragraph and [0094];

> "A "***functional derivative***" of MIS is a compound which ***possesses a biological activity*** (either functional or structural) that is ***substantially similar to a biological activity of MIS***. The term "functional derivatives" is intended to include the "***fragments***", "variants", "analogues," or "chemical derivatives" of a molecule. A "fragment" of a molecule such as … MIS, is meant to refer to ***any polypeptide subset of the molecule.*** Fragments of MIS which as activity and which are soluble (i.e. not membrane bound) are especially preferred". (Emphasis added in bold italics).

In paragraph [0059] of the specification, Applicants teach:

> "It should be understood that the DNA sequence coding for MIS or the C-terminal fragments of MIS that are inserted into the selected site of a cloning expression vehicle can include … only a ***fragment of the actual gene***". (Emphasis added in bold italics).

Accordingly, Applicants respectfully submit the specification teaches one skilled in the relevant art to identify fragments of MIS which can be used in the present invention. However, to expedite the prosecution, Applicants have amended the claims to clarify a fragment of MIS is one in which has a *substantially similar biological activity of MIS*, as taught in paragraphs [0046], [0081], [0083] and [0094] of the specification. The specification teaches methods to identify MIS fragments with similar biological activity of MIS, for example, using the assays discussed in the Examples, such as paragraphs [0194] to [0200], and [0204] to [0207].

The Examiner has also rejected claims 9 and 26 for reciting the genus of C-terminal fragments comprising 108 or more amino acids at the C-terminal. As stated in the Response dated April 26, 2007, Applicants teach, in paragraph [0050] that the C-terminal amino acid nucleotide sequences for human MIS are shown in Figure 18 of U.S. Patent Application 5,661,126 which is incorporated in its entirety by reference. The Figure legend for Figure 18 in the '126 patent discloses "FIG. 18 shows the amino acid (SEQ ID NO: 4) and nucleotide (SEQ ID NO: 3) sequences of human MIS C-terminal fragment, having about 109 amino acids" (see column 8, lines 56-58).

In addition, in paragraphs [0048] of the present specification teaches that the C-terminal fragment as a 12.5 kDa (or 25 kDa under non-reducing conditions) C-terminal fragment of MIS resulting from proteolytic (e.g. plasmin) cleavage at residue 427 of the intact 535 amino acid human MIS monomer. Applicants respectfully submit that the amendments to claims 9 and 26 to amend the fragment to *109* amino acids is disclosed in the original specification and have obviated the rejection.

In view of the foregoing, Applicant respectfully request favorable reconsideration of the application.

The Commissioner is authorized to charge any fee deficiencies or credit any overpayments associated with this submission to the Nixon Peabody LLP Deposit Account No: 50-0850.

The Examiner is invited to contact the undersigned if further matters need to be discussed in order to expedite the prosecution of the present application.

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Respectfully Submitted,

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